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July 1998

Ambient Water Quality Criteria for the Protection of Human Health: Hexachlorobutadiene (HCBD)

NOTE TO READER

The Agency is intending to develop streamlined criteria documents which focus on critical toxicological and exposure-related studies only. This is a departure from the past format in which all existing toxicological and exposure studies were presented and evaluated in the 1980 criteria documents, with equal emphasis placed on exposure, pharmacokinetics, toxicological effects, and criterion formulation. Due to limited resources and a need to update criteria as quickly as possible, EPA has decided to develop more abbreviated versions of criteria documents with an emphasis on using existing risk assessments (on IRIS or other EPA health assessment documents) where available and still relevant, and focusing to a greater extent on pertinent exposure and toxicological studies which may influence the development of a criterion (e.g., critical effects studies which form the basis of RfD development or cancer assessment). EPA will continue to conduct a comprehensive review of the literature for the latest studies, but will not provide a summary or an evaluation of those studies in the criteria documents which are deemed less significant in the criteria development process. Where there is a significant amount of literature on an area of study (for instance, pharmacokinetics), EPA, to the extent possible, will reference the information or cite existing documents (e.g., IRIS or other existing EPA risk assessment documents) which discuss the information in greater detail.

The overall objective of this change in philosophy is to allow EPA to update 1980 AWQC at a greater frequency, while still maintaining the scientific rigor which EPA requires when developing an AWQC. EPA believes these "new" criteria documents will be just as informative as previous criteria documents and will continue to serve as the key scientific basis for State and Tribal standards. EPA also believes the documents will provide the necessary scientific content and scope to allow a State or Tribe to come to an appropriate technical and/or policy decision with regard to setting water quality standards.

EPA requests that commenters identify any relevant information missing from this criteria document which may result in a different criteria calculation or scientific interpretation. EPA also requests comments on the change in criteria document format. This criteria document has undergone extensive external peer review.

1. BACKGROUND

Criteria for hexachlorobutadiene were set in 1980 based on non-threshold carcinogenic effects (45 FR 79318). Because of these non-threshold carcinogenic effects, the levels of

hexachlorobutadiene in water should ideally be zero. However, because the level may not be attainable, the following criteria were set based on three incremental increases in cancer risk.

Risk Level	Criterion (µg/L)	
	Ingestion of Water and Aquatic Organisms	**Ingestion of Aquatic Organisms**
10^{-5}	4.47	500
10^{-6}	0.45	50
10^{-7}	0.045	5

Under the National Toxics Rule (USEPA, 1992), the criteria were updated to reflect a new cancer potency factor. At a risk level of 10^{-6}, the criterion for ingestion of water and organisms is 0.4 µg/L and for ingestion of organisms only, the value is 50 µg/L. These values are essentially the same as the values set in 1980.

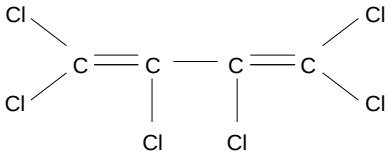
This criteria document updates the criteria for hexachlorobutadiene using new methods and new information described in the *Federal Register* notice to calculate ambient water quality criteria. These include new methods to determine toxicity dose-response relationships for both carcinogenic and noncarcinogenic effects, updated exposure factors (e.g., values for fish consumption), new exposure assumptions used in the calculation, and new procedures to determine bioaccumulation factors. The Technical Support Document (TSD) accompanying the *Federal Register* notice describes these methods in greater detail. In addition to the new methods and information described above, new information on toxicity, exposure, and bioaccumulation of hexachlorobutadiene is also included in this update.

Based on the most sensitive end point (cancer), the proposed criterion is 0.11 µg/L or 0.12 µg/L to protect against ingestion of drinking water and aquatic organisms, or ingestion of aquatic organisms alone (including incidental water ingestion from recreational activities), respectively. The value is based on the kidney toxicity, which is believed to be the precursor leading to tumor formation. The calculation is based on adults in the general population.

The following sections include the toxicological, exposure, and bioaccumulation factor evaluations, and the calculation of the hexachlorobutadiene criteria.

2. CHEMICAL NAME AND FORMULA

The AWQC are being derived for hexachlorobutadiene (CAS No. 87-68-3).



Synonyms include the following: HCBD, C 46, Dolen-Pur, GP-40-66:120, hexachlorobutadiene, perchloro-1,3-butadiene, perchlorobutadiene, 1,3-hexachlorobutadiene, 1,1,2,3,4,4-hexachloro-1,3-butadiene, RCRA Waste Number U128, UN 2279.

Chemical and Physical Properties (Callahan et al., 1979; Banerjee et al., 1980; U.S. EPA, 1980; Hawley, 1981; Ruth, 1986; NTP, 1998)

Chemical Formula	C_4Cl_6
Molecular Weight	260.7
Physical State (25°C)	Clear, colorless liquid
Boiling Point (at 25 mm Hg)	210 to 220°C
Melting Point	-19 to -22°C
Density (20°C)	1.68 g/mL
Vapor Pressure (20°C)	0.15 mm Hg
Specific Gravity (15.5°C)	1.675
Water Solubility (20°C)	Insoluble
Log Octanol Water Partition Coefficient	3.74
Odor Threshold (air)	12 mg/m^3
Conversion Factor	1 ppm = 10.66 mg/m^3 1 mg/m^3 = .0938 ppm

3. SUMMARY OF PHARMACOKINETICS

There are limited quantitative pharmacokinetic data on HCBD and all available data are from animal studies. Single oral doses were readily absorbed at a low dose of 1 mg/kg, but absorption was incomplete at a high dose of 50 mg/kg. At the high dose, a higher percentage of the labeled HCBD was excreted unchanged in the feces (69% at the high dose compared to 42% at the low dose), and there was a lower renal excretion of metabolites (11% of the administered dose at the high dose compared to 31% at the low dose). This was attributed to an early saturation of the compound in the high dose group (Reichert et al., 1985). HCBD is initially transported to the liver, where it is conjugated with glutathione (Garle and Fry, 1989). This conjugate is excreted in the bile and transported intact or as the cysteine conjugate to the kidney (Dekant et al., 1990). There the conjugate can be transformed to S-(pentachlorobutadienyl)-

cysteine (PCBC), which can be converted by a lyase to the reactive intermediate tetrachlorobutadienylthioketene. Alternatively, following N-acetylation in renal tubular cells, mercapturic acid is formed and excreted in urine. Other metabolites are also formed via deamination and subsequent decarboxylation of the cysteine adduct. HCBD and its metabolites are excreted both in the urine and feces (Reichert et al., 1985, Nash et al., 1984).

Detailed information was not located on the half-life of HCBD. The short-term organ repositories of HCBD are indicated by a study that found the highest concentrations in the kidney, liver, and brain of Wistar rats three days after dosing (Reichert, 1983). Long-term sites of deposition are not known.

4. Toxicological Basis for Criterion

4.1 Noncancer Data and Previous Evaluations

An NTP sponsored study of HCBD was reported in Yang et al. (1989) and NTP (1991).[1] This includes both two-week and 13-week dietary studies with B6C3F1 mice. The two-week study received 0, 30, 100, 300, 1,000 or 3,000 ppm HCBD. Toxic responses were found primarily in the higher dose groups. These responses included abnormal clinical signs, mortality, body and organ weight depression, and gross and histopathological changes. The most prevalent microscopic lesion, seen in all HCBD-treated mice of both sexes, was renal tubular cell necrosis and/or regeneration. Regeneration was seen only in the lower dose groups. The 13-week study of male and female B6C3F1 mice received doses of 0, 1, 3, 10, 30, or 100 ppm (0, 0.1, 0.4, 1.5, 4.9 or 16.8 mg/kg-day for the males and 0, 0.2, 0.5, 1.8, 4.5, or 19.2 mg/kg-day for the females). Body weight gain was reduced in the 30- and 100-ppm males, and the 100-ppm females. Significant reduction in kidney weights was seen in the 30- and 100-ppm males and 100-ppm females. Treatment-related increase in renal tubular cell regeneration was seen in both the males and females (Table 4.1.1). This lesion was characterized by an increase in both the number and the basophilic staining intensity of the tubular cells; severity increased with dose. Female mice appeared more susceptible than male mice. A statistically significant increase in responses was seen at 0.5 mg/kg-day, with a NOAEL of slightly less than 0.2 mg/kg-day (one out of 10 females responded at 0.2 mg/kg-day). The study also found a 12% decrease in heart weights in the highest exposure group.

The Kociba et al. (1977) study (also discussed below in the cancer section) evaluated Sprague-Dawley rats orally dosed with 0, 0.2, 2 or 20 mg/kg-day for 22 to 24 months. (In this paper, the authors reported a previous 30-day dietary study in their laboratory in rats receiving HCBD at doses ranging from 1 to 100 mg/kg. The kidney appeared to be the organ most sensitive to the toxicity of HCBD. Renal toxicity in the form of an increase in the kidney-body ratio, as well as renal tubular degeneration, necrosis and regeneration was observed in rats

[1]The human equivalent dose was calculated using the new proposed approach of scaling by raising body weight to the 3/4 power.

receiving 30, 65 and 100 mg/kg-day). In the two-year study, mortality in the males was increased with increasing dose (Fig.1). The increase in the mortality was statistically significant for males ingesting 20 mg/kg-day of HCBD during the last 2 months of the study. The ingestion of 20, but not 2 or 0.2 mg/kg-day of HCBD, caused a significant depression of the body weight gain of both male and female rats (Table 4.1.2). This decrease in body weight was noticed early in the experiment. It was significantly decreased from day 27 through day 512 in the females and from day 69 through day 671 in the males. The extent of body weight decrease was greater than 10% from day 183 through day 671 in the males and from day 332 through day 512 in the females at the highest dose. Kidney toxicity was manifest by increased excretion of coproporphyrin (Table 4.1.3) and renal tubular epithelial hyperplasia in the two highest dose groups. The increased excretion of coproporphyrin was statistically significant in males ingesting 20 mg/kg-day of HCBD for 12 months, and in females ingesting 2 mg/kg-day of HCBD for 14 months. After 22 months, males ingesting 20 mg/kg-day HCBD had a slight, but statistically significant, depression of the red blood cell count (Table 4.1.4). The relative and absolute weights of kidneys of males ingesting 20 mg/kg-day of HCBD were statistically increased. In addition, the authors reported that multi-focal or disseminated renal tubular epithelial hyperplasia in rats ingesting 20 and possibly 2 mg/kg-day of HCBD was seen. This was observed in some of the rats examined from the 13th to the 24th month of the study. Focal adenomatous proliferation (a more advanced stage of hyperplasia) of renal tubular epithelial cells was also noted in the kidneys of some males ingesting 20 mg/kg-day of HCBD, and some females ingesting 20 or 2 mg/kg-day of HCBD. A NOAEL of 0.2 mg/kg-day was identified in the study for a lack of kidney toxicity and hyperplasia.

Table 4.1.1
Incidences of Renal Tubular Regeneration in B6C3F1 Mice following 13-week Dietary Exposure to HCBD*

Male		Female	
Dose (mg/kg-d)	Incidence†	Dose (mg/kg-d)	Incidence†
0	0/10	0	0/10
0.1	0/10	0.2	1/10
0.4	0/10	0.5	9/10
1.5	0/9	1.8	10/10
4.9	10/10	4.5	10/10
16.8	10/10	19.2	10/10

* Source: NTP, 1991; Yang et al., 1989.
† No. of Mice with Lesion/Total No. Examined

Table 4.1.2 Mean Body Weight For Rats Maintained on Diets Containing HCBD*

Dose (mg/kg/day)	Mean Body Wt. , ♂ grams (Mean ± S.D.) On Day 512	Mean body Wt., ♀ grams (Mean ± S.D.) On Day 512
0	633 ± 36	393 ± 41
0.2	613 ± 64	374 ± 33
2.0	610 ± 78	402 ± 66
20.0	550[a] ± 31	351[a] ± 22

* Source: Kociba et al, 1977
[a] statistically significant decrease from control mean, $p<0.005$

Table 4.1.3 Mean Values for Urinary Excretion of Coproporphyrin for Rats Of Two Year Toxicity Study of HCBD*

Dose Level (mg/kg/day)	Coproporphyrin (g/24 hours) Mean ± S.D. ♂	Coproporphyrin (g/24 hours) Mean ± S.D. ♀
0	10.2 ± 8.5	5.6 ± 2.4
0.2	14.2 ± 2.6	6.2 ± 3.3
2.0	18.8 ± 2.4	10.6[a] ± 2.4
20.00	23.1[a] ± 11.8	8.4 ± 2.5

* Source: Kociba et al., 1977
The samples were collected on days 377-378 for males and on days 427-428 for females.
[a] Increased significantly from control mean. P<0.05

Table 4.1.4 Mean Hematology Values for Male Rats Maintained on Diets Containing HCBD for 22 months*

Dose Level mg/kg/day	RBC $x10^{4/}/mm^3$	Standard Deviation
0	7.84	±0.54
0.2	7.09	±0.88
2.0	7.74	±0.55
20.0	6.25[a]	±1.45

* Source: Kociba et al, 1977
a statistically significant decrease from control mean, p<0.005

A study by Harleman and Seinen (1979) found liver weight and cytoplasmic basophilia were increased at doses of 6.3 mg/kg-day and higher among weanling rats receiving HCBD orally for 13 weeks. In a 4-week study the same researchers also found ataxia, demyelination and degeneration of the femoral nerve fiber at 150 mg/kg-day.

Harleman and Seinen (1979) reported limited information on reproductive outcomes in female rats orally dosed at 15 and 150 mg/kg-day. No conception was reported in the high dose

group. Lower birth weight and reduced growth were observed in the 6 female offspring of the low dose group.

A rat dietary developmental toxicity study by Schwetz et al. (1977) used doses of 0.0, 0.2, 2, and 20 mg/kg-day for 90 days before mating, 15 days during mating and throughout gestation (22 days) and lactation (22 days). Fetotoxicity was observed 21 days postnatally in the form of decreased body weight at a maternal dose of 20 mg/kg-day. No teratogenic or embryo toxic effects were reported.

The EPA Reference Dose (RfD) Work Group calculated a new RfD and prepared a new RfD summary which was tentatively verified in 1993, but is not yet been loaded on IRIS. This summary identifies renal toxicity as the critical noncarcinogenic effect of chronic low level HCBD exposure. The NOAEL of 0.2 mg/kg-day from the NTP study (1991) was used to calculate a chronic oral exposure RfD. "An uncertainty factor of 1000 was chosen: 10 each for intraspecies extrapolation, interspecies extrapolation and data base deficiencies. A factor of 10 is given for data base deficiency, because there is a potential for reproductive effects and there is a lack of a 2-generation reproductive study." This yields an RfD of 2×10^{-4} mg/kg-day (U.S. EPA, 1993).

4.2 Cancer Evaluation

4.2.1 Human data

No human studies are available for HCBD.

4.2.2 Animal data

4.2.2.1 Inhalation Exposure

No animal studies are available on inhalation exposures to HCBD.

4.2.2.2 Oral Exposure

In a study by Kociba et al. (1977) Sprague-Dawley rats were orally dosed with 0, 0.2, 2 or 20 mg/kg-day HCBD (99% pure) in the diet for 22 to 24 months. Neoplastic changes were found only at the highest dose where a significant increase in mortality (males) and decrease in body weights (both sexes) as well as other severe renal toxicity were observed (See also Section 4.1, Noncancer Data). At the high dose, renal tubular adenomas and carcinomas developed in 6/40 (15%) of females and 9/39 (23%) of males (See Table 4.2.1a-b).

In the Kociba et al. (1977) 2-year dietary study, multiple toxicological effects, including decreased body weight gain (more than 10% depression in both male and female rats), increased mortality, increased urinary excretion of coproporphyrin, increased weights of kidneys, increased renal tubular hyperplasia, and renal tubular adenomas and adenocarcinomas (some of which

metastasized to the lungs), were found in rats exposed to 20 mg/kg-day of HCBD for up to 2 years; lesser degrees of toxicity, including an increase in urinary coproporphyrin excretion and an increase in renal tubular hyperplasia were found in rats ingesting 2 mg/kg-day of HCBD for up to 2 years; and no discernable effects were seen in rats ingesting 0.2 mg/kg-day for up to 2 years. Progressive toxicological changes in the kidney occurred over time: kidney organ weight changes, increased excretion of coproporphyrin, renal tubular degeneration, necrosis, regeneration, hyperplasia, focal adenomatous proliferation, and tumor formation. (A composite dose-related change in the rodent kidney leading to tumor formation is shown in Table 4.2.2). Thus, the data as a whole suggest that the renal tumor formation may result from cytotoxicity induced by exposure to HCBD.

The tumorigenicity is not associated with the accumulation of α-2u-globulin. For example, unlike predicted by the α-2u-globulin mechanism (i.e., the tumors appear in the male rats only), renal tubular tumors appeared in both male and female rats in the chronic study. In addition, oral exposure of rats to HCBD (100 mg/kg-day for 5 days) did not result in the accumulation of α-2u-globulin in the kidney of rats (Saito et al., 1996).

Table 4.2.1a Lifetime Oral Exposure Study: Tumor Data in Male Rats

Administered Dose (mg/kg-d)	Human Equivalent Dose Using Body Weight$^{3/4}$ Scaling (mg/kg-d)	Renal Tubular Neoplasm Incidence[2]
0	0	1/90
0.2	0.062	0/40
2.0	0.62	0/40
20	5.80	9/39

Table 4.2.1b. Lifetime Oral Exposure Study: Tumor Data in Female Rats

Administered Dose (mg/kg-d)	Human Equivalent Dose Using Body Weight$^{3/4}$ Scaling (mg/kg-d)	Renal Tubular Neoplasm Incidence[3]
0	0	0/90
0.2	0.054	0/40
2.0	0.55	0/40[4]
20	5.31	6/40

The administered doses and the tumor incidence data are from the Kociba et al.(1977) study; the human equivalent doses are calculated using the scaling factor of body weight raised to the 3/4 power as shown below:

Human Equivalent Dose = (Animal Dose){(Animal Body weight)/Human Body weight)}$^{1/4}$.

[2] The incidence indicates the number of animals with one or more renal tubular neoplasm over the total number of animals studied.

[3] The incidence indicates the number of animals with one or more renal tubular neoplasm over the total number of animals studied.

[4] Hyperplasia (multi focal or disseminated renal tubular epithelial) and focal adenomatous proliferation (in the renal tubular epithelial cells) were noted in females at this dose level. These effects are not tumors, but are considered to be changes that often lead to tumors.

Table 4.2.2*
Dose-Related Changes in the Rodent Kidney after Oral Exposure to HCBD
***Chronic Study* - Rat (Kociba et al., 1977)**

Dose (mg/kg/d) ***Chronic*‡**	**0.2**	**2**	**20**
coproporphyrin increase	–	+ (♀ only)	+
terminal kidney weight increase (abs. & rel.)	–	–	+
hyperplasia - multi focal	–	?	+
hyperplasia-adenomatous	–	+ (♀ only)	+
tumors	–	–	+

Subchronic Study - Mouse (NTP, 1991; Yang, et al., 1989)

	Dose (mg/kg/d)				
	0.1-0.2	0.4 - 0.5	1.5-1.8	4.5-4.9	16.8-19.2
kidney weight decrease (abs. and rel.).	–	–	–	+ (♂ only)	+
tubular regeneration	? (1/10 ♀)	+ (♀ only)	+ (♀ only)	+	+

* This is a composite table of a chronic rat study (Kociba et al. , 1977), shown on top, and a subchronic mouse study at the bottom (NTP, 1991, Yang et al.,1989)

‡ The dose in the chronic rat study is shown in italic, and the dose in the subchronic mouse study is underlined.

4.2.3 Other Key Data

Mutagenicity

Data regarding the mutagenicity of hexachlorobutadiene are mixed. Rapson et al. (1980), Reichert et al. (1983), Stott et al. (1981), and DeMeester et al. (1981) reported that HCBD was not mutagenic in the *Salmonella typhimurium* reverse mutation assay with or without the addition of rat liver homogenate (S9). Reichert et al. (1984) showed that HCBD induced gene mutation in the presence of GSH, and Simmon (1977) reported that HCBD was mutagenic in *S. typhimurium* with an S9 activation system.

HCBD caused an increase in unscheduled DNA synthesis in Syrian hamster embryo fibroblasts in both the presence and absence of an exogenous metabolizing system. Morphological transformation was also induced (Schiffmann et al., 1984). HCBD was not mutagenic in *Drosophila* by feeding or injection (Woodruff et al., 1985).

An *in vivo* study of rats orally dosed with 20 mg/kg-day for 3 weeks resulted in a 1.8 fold increase in renal DNA synthesis and a 1.4 fold increase in renal DNA repair. A small amount of DNA alkylation was also observed in the kidney of HCBD exposed rats (Stott et al., 1981).

Structural Analogue and Metabolite Data

HCBD is initially transported to the liver where it is conjugated with glutathione (Garle and Fry, 1989). This conjugate is excreted in the bile and transported intact or as the cysteine conjugate to the kidney (Dekant et al., 1990). There the conjugate can be transformed to *S*-(pentachlorobutadienyl)-cysteine (PCBC), which can be converted by a beta-lyase to the reactive intermediate tetrachlorobutadienylthioketene. Limited data (Lock, 1994) showed that the ability of renal cortical beta-lyase of human to metabolize PCBC to reactive metabolite may be much lower than that of rat weakening the genotoxic concern.

Metabolites and derivatives of HCBD were mutagenic in *S.typhimurium* with metabolic activation (Wild et al., 1986; Green et al., 1983; Reichert and Schutz, 1986). Some metabolites of HCBD bind preferentially to mitochondrial DNA rather than nuclear DNA in kidney cells (Shrenk and Dekant, 1989). A sulfoxide metabolite has been observed via one pathway (Birner et al., 1995) of the males that may have the potential to bind to macromolecules. Other studies also suggest reactive or mutagenic metabolites (Garle and Fry, 1989; Schiffman et al., 1984).

4.2.4 Background/Previous Evaluation

The IRIS file contains a carcinogenicity assessment of HCBD (IRIS, 1996, verified 11/12/86). Based on the appearance of renal neoplasms in male and female rats at one high dose in one species, hexachlorobutadiene was classified as a possible human carcinogen (Group C). Using the male rat data shown in Table 4.2.1a above (Kociba et al. (1977), a rat lifetime of 770 days and an average rat

weight of 0.610 kg, a cancer potency factor of 7.8 x 10^{-2} $(mg/kg\text{-}day)^{-1}$ was calculated using the linearized multistage model and a scaling factor of body weight raised to the 2/3 power.

A carcinogenic risk evaluation for inhalation exposure used the same data set to calculate a unit risk of 2.2 x 10^{-5} $(\mu g/m^3)^{-1}$.

4.2.5 Cancer Risk Evaluation Using the New Proposed Methodology

The proposed revision of the methodology for deriving ambient water quality criteria is consistent with the principles of the methodology discussed in the proposed cancer guidelines and the *Federal Register* notice and Technical Support Document from EPA's Office of Water to evaluate and describe the carcinogenicity of chemicals (USEPA 1996, USEPA 1998a, USEPA 1998b).

Based on renal tumor finding in one chronic feeding study at one high dose in one species (both sexes of Sprague-Dawley rats) by the oral route, HCBD is considered likely to be carcinogenic to humans.

4.2.5.1 Mode of Action Considerations and Rationale for Selecting the Cancer Assessment Approach

The mode of action for the tumorigenesis of HCBD in animals is not clear. Limited data on mode of action suggest HCBD-induced cytotoxicity may lead to tumor formation (Kociba et al., 1977; Dekant et al., 1990; Lock, 1994). There are no human data; the only oral carcinogenic study in rats shows kidney tumors at a very high dose where the MTD has been exceeded (i.e., there is increased mortality, greater than 10% decrease in body weight and severe renal toxicity). Studies in rats and mice indicate that kidney is the target organ. Progressive toxicological changes are observed in kidney over time: decreased and increased kidney weight, increased excretion of coporphyrin (kidney dysfunction), renal tubular degeneration, necrosis, and regeneration, hyperplasia, focal adenomatous proliferation, and finally tumor formation.

In vitro studies (Schnellman et al., 1987; Groves et al., 1991; Jones et al., 1986; and Wallin et al., 1987) indicate that mitochondria of the renal tubular epithelial cells be the major target of toxicity induced by HCBD metabolites in the kidney. Mitochondrial dysfunction which is likely to be one of the earliest observed effect, may result from the interaction of reactive metabolites with mitochondrial membrane. However, in the presence of metabolic activation, HCBD and its reactive metabolites, are also mutagenic in some (Simmon, 1977; Reichert et al, 1984; Reichart and Schutz, 1986; Wild et al., 1986), but not all studies (See mutagenic section). Thus, a mutagenic mode of action can not be ruled out (Dekant et al., 1990; Lock, 1994). Recent data (McCarthy et al., 1992) showed that the ability of renal cortical β-lyase of humans to metabolize *S*-(pentachlorobutadienyl)-cysteine (PCBC) to the reactive intermediate may be more than a magnitude lower than that in the rat; thus there may be decreased concern over genotoxicity for humans. Nevertheless, both linear (mutagenic) and nonlinear (toxicity associated) approaches may be operating *in vivo*. Therefore, both approaches are presented for risk assessment at very low doses. However, for the derivation of

AWQC, the nonlinear approach is selected. The rationale is that in this specific case, there is too much uncertainty and not enough confidence using the tumor data (only one data point at a very high dose where the MTD has been exceeded and toxicity is severe) to do a linear high to low dose extrapolation for the estimation of human risk. Moreover, one has more confidence in the data base to do a nonlinear approach since data from both rats and mice support the same NOAEL value.

4.2.5.2 Hazard Characterization

The subchronic and chronic rodent studies present a consistent picture of kidney toxicity with a dose-related progression of subclinical signs of kidney damage, followed by cellular necrosis and regeneration, and tumor formation at the highest dose in both male and female rats. Tumors were observed only in the kidney. This strongly suggests that tumorigenesis is secondary to organ toxicity. Nevertheless, the data set must be considered as too limited to support a conclusion of high confidence. Only one chronic study (rats) is available. The dose spacing (a ten-fold spacing between the highest and next lower dose) allows no opportunity to observe whether tumorigenesis is only associated with cytotoxicity. There are no studies of cell proliferation. There are limited data on mutagenicity (mostly *in vitro*) which indicated that the compound's metabolites may be mutagenic; the observation that a lyase present in the kidneys of rats and humans metabolize the compound to a reactive metabolite may be significant. Given the limitations of the data base on the mode of action, but considering the strong suggestion that the only site at which tumors were observed is the target organ of toxicity, the dose response assessment should include both linear and nonlinear approaches.

4.2.5.3 Cancer Risk Evaluation[5]

Nonlinear MOE Approach

Identification of a Point of Departure (Pdp) for Compound HCBD

The cancer risk for oral exposure to HCBD was assessed by following the steps outlined in the FR notice (USEPA, 1998a) and the related Technical Support Document (USEPA, 1998b). The study used was on the renal toxicity-induced progression of pathology leading to renal tumor formation in the male and female rats (Kociba et al., 1977, See Sections 4.1 and 4.2 above, and Mode of Action (Section 4.2.5.1). The NOAEL for renal toxicity, 0.2 mg/kg-day, was used as the point of departure (Pdp) for the calculation of AWQC for HCBD by the margin of exposure analysis (MOE). Because evidence indicates that carcinogenicity is secondary to renal toxicity; thus, one would consider protection from the renal toxicity will protect from carcinogenicity. In such a case, the MOE analysis for the toxicity becomes an RfD derivation. (See Section 3.1.2. Analysis in the

[5] This section contains a discussion of the derivation of a cancer potency value based on oral exposure to HCBD. The focus of this criteria document is on waterborne exposure and the development of AWQC. While the contribution to cancer risk from air sources may be important, it is not the primary subject of this analysis. Consequently, the inhalation cancer potency value listed in IRIS, and described above, is not re-examined in this analysis.

Range of Extrapolation in the 1996 Proposed Cancer Guidelines in 61 FR 17993, April 23, 1996). (See also the following paragraph for more details).

The human equivalent dose (HED) for the NOAEL of 0.2 mg/kg-day was calculated to be 0.054 mg/kg-day, using the new scaling factor of body weight raised to the 3/4 power (as shown in the Technical Support Document, Equation 2.1.1). This adjusted Pdp (i.e., 0.054 mg/kg-day) was used for the AWQC calculations.

Selection of a Margin of Safety (MOS)

For HCBD, mode of action considerations suggest carcinogenicity being secondary to renal toxicity (See Section 4.2.5.1 above on Mode of Action); and the MOE analysis for the toxicity becomes an RfD derivation. (See Section 3.1.2. Analysis in the Range of Extrapolation in the 1996 Proposed Cancer Guidelines in 61 FR 17993, April 23, 1996).

Based on a consideration of numerous factors such as intraspecies variability (10), inter species variability (3 is used here because animal dose has already been adjusted to HED), and an additional factor of 10 for data base insufficiency, including insufficient data on potential risk to children. Thus, an overall Safety Factor of 300 is used which is considered sufficient for human health protection.

Substituting the Pdp (i.e., 0.054 mg/kg-day), the SF (300) and the other factors (i.e., fish intake, BAF, RSC, etc.) into Equation 7.1.2. in Section 7.1.2., the AWQC is 0.11 µg/L for the ingestion of drinking water and aquatic organisms, or 0.12 µg/L for the ingestion of aquatic organisms alone (including incidental water ingestion from recreational activities).

The New Linear Approach

Since the mortality rate was significantly increased in the male rats exposed at the high dose (which is the only dose with an increased tumor incidence in animals), the tumor data from the female rats were used instead for the risk assessment (See Table 4.2.1b). The human equivalent dose was calculated using the scaling factor derived from body weight raised to the 3/4 power. The dose-response modeling and calculations were carried out as follows:

1) The quantal polynomial model[6] was used to fit the Kociba et al. (1977) tumor dose response data in the observed range. The LED_{10}[7] (the lower 95th percent confidence limit on the dose at which the extra risk is 10%) was calculated to be 2.5 mg/kg-day.

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[6] This modeling was carried out using the Global 86 multistage model software.

[7] Use of the LED_{10} as the point of departure is recommended with this methodology, as it is with the Proposed Cancer Guidelines. Public comments were requested on the use of the LED_{10}, ED_{10}, or other points. EPA is currently evaluating these comments and any changes in the Cancer Guidelines will be reflected in the final AWQC Methodology.

2) linear extrapolation was carried out from the LED_{10} to the origin (the zero dose, zero response point). The slope of this line (i.e., y/ x) was obtained using the following equation:

$$m = \frac{0.10}{LED_{10}}$$

(Equation 4.2.1)

The variable "m" is the low dose cancer potency factor and was calculated to be 4×10^{-2} (mg/kg-day).

3) The risk specific dose (RSD) was calculated for a specific incremental targeted lifetime cancer risk (for example, one in one million or 10^{-6}) using the equation:

$$RSD = \frac{Target\ \ Incremental\ \ Cancer\ \ Risk}{m}$$

(Equation 4.2.2)

where:

RSD	=	risk specific dose (mg/kg-day)
Target Risk	=	10^{-6}
m	=	cancer slope factor of 4×10^{-2} $(mg/kg\text{-}day)^{-1}$

The calculated RSD is 2.5×10^{-5} mg/kg-day for a 10^{-6} (one in a million) lifetime cancer risk. This RSD is substituted into Equation 7.1.2 in Section 7.1.2. For a lifetime risk of 10^{-6}, the AWQC is calculated as 0.046 µg/L for the ingestion of drinking water and aquatic organisms, or 0.049 µg/L for the ingestion of aquatic organisms alone (including incidental water ingestion from recreational activities).

4.2.6 Discussion of Confidence

The available data base associating HCBD and carcinogenicity is incomplete. There are no human data. The evidence is obtained only in one chronic dietary study in a single species (Sprague-Dawley rats, See Kociba et al., 1977) where rats developed severe renal toxicity preceding tumor formation. The tumors were seen only at a high dose which exceeded the maximum tolerated dose (MTD, i.e., greater than 10% body weight depression) in both sexes of rats and high mortality in the

males. Similar renal toxicity observed in a 30-day study of HCBD in rats by the same laboratory and another 90-day subchronic study in mice (NTP, 1991), strengthens the idea that the tumor formation is induced by cytotoxicity. Both the NTP and Kociba et al. (1977) studies tested a sufficient number of animals.

In the Kociba et al. study (1977), the dose selection is too scattered. The dose spacing between 2 mg/kg-day (no tumor response) and 20 mg/kg-day (18% tumor response in the female and 23% response in the males) is too wide (ten-fold). More dose(s) in between 2 and 20 mg/kg-day would better delineate the dose-response curve.

A weight of evidence analysis of the available data as a whole indicate that the confidence in using either linear or nonlinear approach is not high; especially the linear method which is based on only one data point at a high dose exceeding the MTD.

5. EXPOSURE ASSUMPTIONS

5.1 Relative Source Contribution Analysis

When an ambient water quality criterion is based on noncarcinogenic effects or carcinogenic effects evaluated by the margin of exposure (MOE) approach, anticipated exposures from non-occupational sources (e.g., food, air) are taken into account. The amount of exposure attributed to each source compared to total exposure is called the relative source contribution (RSC) for that source. The allowable dose (in this case, the minimum effective dose level divided by a safety factor (Pdp /SF) used in the MOE approach) is then allocated via the RSC approach to ensure that the criterion is protective enough, given the other anticipated sources of exposure. Thus, accounting for non-water exposure sources results in a more stringent ambient water quality criterion than if these sources were not considered. The method of accounting for non-water exposure sources is described in more detail in the FR notice (USEPA, 1998a) and in the TSD (USEPA, 1998b). Available information on exposure sources is discussed below. HCBD is being evaluated based on the MOE approach for carcinogenicity, so an evaluation of the RSC is performed.

The method of determining the RSC differs depending on several factors, including (1) the magnitude of total exposure compared with the Pdp /SF, (2) the adequacy of data available, (3) whether more than one guidance or criterion is to be set for HCBD, and (4) whether there is more than one significant exposure source for the chemical and population of concern. The population of concern for HCBD is described in Section 5.1.1. The sources of exposure to HCBD and estimates of exposure used to determine the RSC for the identified population are discussed in Sections 5.1.2 and 5.1.3. Section 5.1.4 discusses the adequacy of exposure data, and Section 5.1.5 discusses significant sources of exposure for HCBD and presents the RSC estimates for setting the AWQC for HCBD.

5.1.1 Population of Concern

For HCBD, the population of concern for setting national criteria is assumed to be the general population. Issues regarding the selection of the population of concern are described in more detail in Section 5.2 in the context of choosing exposure parameters for the AWQC equation.

5.1.2 Overview of Potential for Exposure

HCBD is released to the environment from anthropogenic sources. It is used as a solvent in chlorine gas production, as an intermediate in the manufacture of rubber compounds and lubricants, and as a pesticide. A search of the Stanford Research Institute Directory of Chemical Producers located no manufacturing facilities for HCBD. However, HCBD is expected to be used in the production of chlorine and is a by-product of chlorinated aliphatic production, including vinyl chloride, carbon tetrachloride, chloroform, and ethylene dichloride.

According to the U.S. Environmental Protection Agency's (EPA) Toxics Release Inventory, the total release of HCBD into the environment in 1990 by chemical manufacturers was 5,591 pounds. The largest pathway of release was emissions into the air, which accounted for 82% or 4,906 pounds. Release of HCBD into surface water accounted for 12% or 715 pounds, and release of HCBD by underground injection accounted for 6% or 330 pounds. There were no releases of HCBD onto land via surface application.

5.1.3 Estimates of Exposure from Different Environmental Media

The following sections describe studies that measured concentrations of HCBD in environmental media, and estimate exposures from these media by combining concentrations with estimates of the amount of each exposure medium (drinking water, food, fish, air) ingested or inhaled. For the targeted general population, central tendency estimates of exposure are most appropriate for each exposure medium.

5.1.3.1. Exposure from Treated Drinking Water and Ambient Waters

Concentrations in Water

Several studies analyzed drinking water for HCBD. The National Screening Program for Organics in Drinking Water (referred to as the National Screening Program) was conducted by SRI International for EPA, from June 1977 to March 1981. Its primary purpose was to establish an analytical protocol to screen for 51 organic compounds in drinking water. Raw and finished water from 169 drinking water systems in 33 states were analyzed. The survey evaluated drinking water samples from surface, ground, and mixed-water supplies. In this survey, an analysis for HCBD was conducted using 141 finished water samples and 149 raw water samples. All the raw and finished water samples had HCBD concentrations of less than the minimum quantification limit of 0.1 µg/L (Borland, 1981).

EPA's Unregulated Contaminant Data Base, which contains drinking water monitoring data reported by the states, was searched for occurrence of HCBD in water. A total of 28 states reportedly monitored for HCBD, with only the states of Alabama, Texas, Ohio, and Tennessee reporting positive results. Results from each state are shown in Table 5.1.1.

Table 5.1.1: Unregulated Contaminant Data Base Results for HCBD

State	Source	Number of Facilities	Number of Positives	Maximum (µg/L)
Alabama	Ground	160	3	1.00
Ohio	Ground	5,747	2	2.00
Tennessee	Unknown	391	1	4.20
Texas	Unknown	2	2	8.00

Levins et al. (1979) reported results from a study of the drainage basin in the R.M. Clayton Sewage District near Atlanta, Georgia. As part of that study, two tap water samples were collected from the area; however, HCBD was not detected above the reporting limit of 10 µg/L. In 1974, EPA conducted a survey that sampled finished water from three municipal water treatment plants in the New Orleans area that draw water from the Mississippi River. Three seven-day composite samples were found to contain HCBD in concentrations ranging from 0.07-0.7 µg/L (Keith et al. 1976). In a 1975 follow-up study, the EPA sampled the drinking water of 10 cities and found HCBD in one sample at a concentration of <0.1 µg/L (USEPA, 1980a). The EPA Office of Toxic Substances sponsored a study of metropolitan locations within the continental United States to compare levels of halogenated organics in various environmental media. In Niagara and Buffalo, New York, six drinking water samples out of 14 tested for HCBD were positive with a range from trace levels to 0.167 µg/L. In the New Jersey area, the average concentration of three drinking water samples was 0.7 µg/L (USEPA, 1979).

In addition to drinking water studies, several surveys analyzed source water. In 1987, the effects of land use on ground-water quality in central Florida were studied by the U.S. Geological Survey in cooperation with the Florida Department of Environmental Regulations. The ground water was sampled in four areas with different land uses; an urban area, a citrus farming area, a phosphate mining area, and a control area. In 32 samples from the four areas, there were no measurable amounts of HCBD in ground water. The detection limit for this study was 5.0 µg/L (Rutledge, 1987).

In another study, HCBD was measured at concentrations of 1.9 and 4.7 µg/L in surface water near Geismar, Louisiana. Samples from an industrial effluent at a site in Geismar found HCBD concentrations ranging from <0.1-4.5 µg/L (USEPA, 1991). At an industrial landfill pond in Louisiana, HCBD was measured at 4.49 µg/L (USEPA, 1980b). The Potomac River at Quantico,

Virginia was also sampled for HCBD but the contaminant was not detected, based on a detection limit of 4 µg/L (Hall et al., 1987). Laseter et al. (1976) reported results from an ecological survey of the Mississippi River between Baton Rouge and New Orleans, Louisiana. Three river samples reportedly contained concentrations of 0.9, 1.4, and 1.0 µg/L. In nine samples taken from inland sites, concentrations ranged from <0.7-1.5 µg/L with a mean and median of 1.0 µg/L.

STORET, operated by EPA, is a computerized data base comprising water quality data collected from states, EPA regional offices, and other governmental agencies. It contains over 130 million observations for over 700,000 sampling sites located throughout the United States. It is important to note that there are limitations in using STORET data to estimate representative concentrations of contaminants in public water systems. The data in STORET were collected from an array of studies conducted for various purposes. Analyses were conducted in different laboratories employing different methodologies with a range of detection limits. In many cases, the detection limits were not reported. In drinking water, there were two positive detections of HCBD in Utah, at levels of 0.3 and 1 µg/L. In ambient water, there were no positive detections reported (USEPA, 1992b).

Exposure Estimates

It is possible to estimate drinking water exposure by using HCBD concentrations in treated drinking water or in ambient surface water. The choice of which concentration data to use may impact the portion of total exposure attributable to the drinking water source and could, therefore, impact the final AWQC that will be set. For the HCBD criterion, the magnitude of the exposure estimate using concentrations of HCBD in drinking water is equivalent to the magnitude of exposure using the ambient water source. Therefore, use of either one will result in the same AWQC.

Central tendency from drinking water intake. Estimating exposure to HCBD from drinking water is complicated by the fact that the two most representative studies/data sources indicate that HCBD was either not detected or was detected in very few samples. An estimate of exposure to HCBD in drinking water was determined using occurrence information from the National Screening Program for Organics in Drinking Water. This study was used because drinking water systems in a fairly large number of states (33) were surveyed, and the detection limit was reported. As indicated above, all finished drinking water samples had concentrations below detection. Assuming that all samples are half the detection limit, exposure for an average individual is estimated to be 1.43×10^{-6} mg/kg-day. This exposure estimate is determined by multiplying the drinking water concentration by daily drinking water intake (2 liters/day) and dividing by average adult body weight (70 kg).

Information from URCIS and STORET (the two other large surveys or compilations of data) were not used because most values were below detection and because the detection limit was not available or reported. Therefore, an assumption about the value of detection in addition to assuming values for the undetected samples would need to be made for these studies.

Incidental water intake. An estimate of the amount of incidental water ingested due to recreational activities is taken into account when setting the AWQC for waterbodies where the criterion is based on fish consumption only. Using half the detection limit and multiplying by the amount of water assumed to be ingested incidentally in situations where individuals use water bodies for recreation (0.01 L), an estimate of 7.14×10^{-9} mg/kg-day was determined for the intake from incidental ingestion.

Central tendency ambient water intake. The National Screening Program for Organics in Drinking Water also sampled untreated water. Again, all of these samples were below the detection limit. Therefore, an estimate of exposure from ambient waters would be equivalent to exposure from finished drinking water, as indicated above.

5.1.3.2 Non-Fish Dietary Exposures

Concentrations

According to the Food and Drug Administration (FDA), there are no approved uses of HCBD either directly or indirectly in foods, including food processing equipment (DiNovi, 1997). FDA also stated that HCBD is not regulated in plastics.

Some information on concentrations of hexachlorobutadiene (HCBD) in different food items is available. One study measured HCBD in food items within a 25-mile radius of tetrachloroethylene and trichloroethylene manufacturing plants which emit HCBD as a waste product (Yip, 1976). HCBD was not detected in 15 samples of eggs and 20 vegetable samples. One of 20 milk samples contained 1.32 mg/kg HCBD, although resampling in the area found no detections in milk. This study reported two detection limits: 0.005 mg/kg for nonfatty foods and 0.04 mg/kg for fatty foods. In the United Kingdom, HCBD has been found at concentrations of 0.00008 mg/kg in fresh milk, 0.002 mg/kg in butter, 0.0002 mg/kg in cooking oil, 0.0002 mg/kg in light ale, 0.0008 mg/kg in tomatoes, and 0.0037 mg/kg in black grapes (IARC, 1979).

Further discussions with FDA suggest that the presence of HCBD in food is likely due to the food contacting contaminated water during some food processing activity (DiNovi, 1997). However, there are no regulations for hexachlorobutadiene in food and no exposure estimates have been developed for this chemical (Kusznesof, 1997). Regarding the summarized data above, there is no clear way to estimate the percent of "fatty foods" in the diet. Kusznesof indicated that the total percent of fat in the diet may be around 30%, but that this may not be the same percent as the percent of overall fatty foods in the diet. Therefore, more than 30% of foods may be considered fatty foods.

Estimates of Hexachlorobutadiene Intakes from Food

As noted above, HCBD has been found in a variety of foods in the United Kingdom. In addition, although it may have been incorrectly measured in milk by Yip (1976), it is also possible that it could be found in measurable quantities in the United States. However, because it was generally

undetected in samples taken from areas where HCBD may be emitted, it can be assumed that, on average, HCBD will not be found at detectable levels. Given this sampling data, along with the fact that HCBD has no approved uses, it is anticipated that there would typically be no chronic exposure to HCBD via non-fish dietary foods. Therefore, the central tendency estimate for HCBD intake from food is assumed to be zero.

A high-end estimate may be made by assuming a concentration of one half the detection limit. Because the percent of fatty or non-fatty foods in the diet is not definitively known, a conservative estimate is made using one half the detection limit of 0.04 mg/kg noted for fatty foods in Yip (1976). This concentration (0.02 mg/kg) is multiplied by an estimate of total food intake of 2.6 kg (using intakes for separate age groups reported in Pennington, 1983) and divided by 70 kg to obtain a total daily intake of HCBD from food of 7.4×10^{-4} mg/kg-day. This estimate is four times the Pdp/SF of 1.8×10^{-4} mg/kg-day (USEPA, 1993). (Using one half the detection limit for non-fatty foods results in an intake of 9.2×10^{-5} mg/kg-day, about half the Pdp/SF.) For the majority of regions of the U.S. in which HCBD is not found, using one half the detection limit will overestimate the amount of HCBD in food.

Because the data on concentrations in food are limited, and because the implications of assuming that HCBD occurs at one half the detection limit for fatty foods are large, further research may be required to refine this estimate.

5.1.3.3 Fish Consumption Exposures

Concentrations

The National Study of Chemical Residues in Fish (NSCRF), conducted by EPA's Office of Water, was undertaken to determine the occurrence of selected pollutants in fish from various locations across the United States. Pollutants were measured in bottom feeding and game fish at nearly 400 sites between 1986 and 1989 (Kuehl et al., 1994). A complete presentation of the study plan and results is contained in a joint Office of Water and Office of Research and Development report (USEPA, 1992). Sites at which pollutants were sampled included targeted sites near potential point and nonpoint pollution sources, background sites in areas generally without pollution sources, and a few sites from the U.S. Geological Survey's National Stream Quality Accounting Network (NASQAN) to obtain nationwide coverage. Targeted sites were chosen near areas of significant industrial, urban, or agricultural activities, including more than 100 sites near pulp and paper mills.

Fish species chosen for sampling were routinely consumed by humans and/or bioaccumulative species. At most locations, the NSCRF analyzed one composite sample of bottom-feeding fish, usually composed of whole-body samples. Some bottom fish composite samples were composed of fillets. Composite samples of game fish, composed of fillets were usually taken from areas where whole-body concentrations were high. Each composite sample contained approximately three to five adult fish of similar size from the site. Pollutant concentrations were measured in units of wet weight (USEPA, 1992).

HCBD was detected in fish at 3 percent of the 362 sites sampled. Fillet samples were taken from 106 sites[8]. The mean and standard deviation of HCBD fish concentrations at all sites were 0.6 ng/g and 8.7 ng/g, respectively (Kuehl et al., 1994). These statistics represent the overall mean from all samples, not just from the positive samples. Concentrations were above 2.5 ng/g at only four sites, which were all near organic chemical manufacturing plants (USEPA, 1992). Concentrations and locations of these four sites are:

Concentration (ng/g)	Type of Sample	Location
164.0	Sea Catfish - Whole Body	Louisiana
23.0	Sea Catfish - Whole Body	Texas
10.50	Catfish - Fillet	Illinois
2.54	Catfish - Whole Body	Louisiana

For HCBD, the methods for determining the mean and standard deviation and accounting for non-detects were not specifically stated by EPA (1992) or Kuehl et al. (1994). However, for contaminants that were found at >10% of sites, detailed analyses of concentrations at different types of sites were presented in U.S. EPA (1992). For these sites, non-detected values were set at zero and the maximum concentration at each site was used. Therefore, it is likely that, for HCBD, the non-detects were also set at zero. The value of the detection limit for HCBD was not given in U.S. EPA (1992) or Kuehl et al. (1994). Although EPA presents raw data for many chemicals, the raw data for HCBD were not presented.

Central Tendency Exposure Estimate

Calculating a central tendency estimate is not possible due to the lack of information on detection limits. A crude estimate of exposure can be made with the data from Kuehl et al. (1994). Because these data were taken from many monitoring stations throughout the United States, the estimate may reasonably be indicative of the magnitude of HCBD intake from fish consumption when it is present in fish tissue. An estimate of exposure was determined by multiplying the mean concentration of 0.6 ng/g from the Kuehl et al. data by a fish intake of 18 g for the general population and dividing by adult body weight (70 kg). The resulting estimate, expressed in mg/kg-day, is 1.54×10^{-7} mg/kg-day. As is shown in Table 5.1.2, although this is likely to be a very conservative assumption given the low frequency of occurrence, it is helpful as it indicates the extremely small contribution to total exposure.

[8]It is not clear what the total number of samples was for this study. If one sample of bottom-feeding fish was taken from all sites, then the total number of composite samples was most likely 468.

5.1.3.4 Respiratory Exposures

Concentrations in Air

The largest compilation of data on ambient air concentrations is available from Shah and Heyerdahl (1988). Shah and Heyerdahl compiled ambient air monitoring data from 1970 to 1987 for volatile organic compounds. A total of 72 observations from six studies were reported for HCBD. In cases where more than one sample was taken per day, the concentrations were, in general, averaged and weighted by sampling time when the sampling time varied throughout the day. When more than one sample was included in the average, values less than the minimum quantifiable limit (MQL) were included as one half the MQL when the MQL was given. If the MQL was not indicated in the study used in Shah and Heyerdahl, the values less than the MQL were included as zeros in the average. If the resulting average was less than the MQL, a zero was included. If the average was greater than the MQL, the calculated average was used.

The average and median of all ambient HCBD concentrations were 0.036 ppb (0.42 $\mu g/m^3$) and 0.003 ppb (0.04 $\mu g/m^3$), respectively. The 25th and 75th percentiles were 0.001 ppb (0.01 $\mu g/m^3$) and 0.006 ppb (0.07 $\mu g/m^3$). Median values only were reported for urban areas and source dominated areas. Of 56 samples taken from urban areas, the median was 0.003 ppb (0.04 $\mu g/m^3$). Of 16 samples taken from source dominated areas, the median was 0.002 ppb (0.02 $\mu g/m^3$). No indoor concentrations were reported (Shah and Heyerdahl, 1988).

Shah and Heyerdahl's compilation included a study by Pellizzari et al. (1979), who surveyed the occurrence of halogenated hydrocarbons in various environmental media of five metropolitan areas. As part of this study, HCBD concentrations in the vapor phase of ambient air of four sites were compiled from other research programs, as well as from monitoring conducted specifically for this project. In the Niagara Falls and Buffalo, New York area, concentrations were found to range from trace levels to 0.389 mg/m^3, with six of 15 determinations (40%) containing detectable levels. In the Baton Rouge, Louisiana area, two of 11 determinations (18%) were positive, with concentrations of 0.018 and 0.037 mg/m^3. Sampling in Houston, Texas, and surrounding areas had a range of trace levels to 2.066 mg/m^3 with seven positive values of a total of 17 determinations (41%). (As noted, this study is also included in data cited by Shah and Heyerdahl, 1988).

Class and Ballschmiter (1987) reported that the troposphere of the Northern Hemisphere contains an average concentration of 0.17 ppt (0.002 mg/m^3) at 18 locations sampled from 1982 to 1986. The detection limit was between 0.01-0.1 ppt.

HCBD concentrations in ambient air were measured in two studies included in a compilation of ambient monitoring data for the Urban Area Source Program (USEPA, 1994a). In Columbus, Ohio, which measured HCBD in 1989, concentrations were reported at a minimum detection level of 0.54 mg/m^3 at six monitoring stations. The second survey was conducted in Cincinnati, Ohio, from 1989 to 1991, and detected HCBD at one monitoring site at a concentration of 1.0 mg/m^3.

Central Tendency Exposure Estimate

Because the data from Shah and Heyerdahl (1988) included a fairly large number of observations (72), they were used to calculate an estimate of exposure. However, it is again not possible to calculate a central tendency value for these data due to the lack of information on detection limits. The mean concentration of 0.42 $\mu g/m^3$ from Shah and Heyerdahl (1988) was multiplied by an average air intake of 20 m^3, divided by an adult body weight of 70 kg, and converted from µg to mg, resulting in an intake of 1.2×10^{-4} mg/kg-day. The estimate may be indicative of the magnitude of HCBD intake from air in urban and source dominated areas where it is present. It should be noted, however, that these concentration data are older than data from the Urban Area Source Program (USEPA, 1994a) and Class and Ballschmiter (1987). In addition, the number of geographic areas sampled throughout the United States by Shah and Heyerdahl is not indicated.

5.2 Exposure Data Adequacy and Estimate Uncertainties

After identifying relevant exposure pathways and obtaining available data for quantifying exposure via each pathway, it is important to consider whether the data are adequate to describe exposure estimates for each exposure medium. The adequacy of exposure data, in part, determines the specific method with which the RSC estimates will be determined. See the FR notice and TSD for more discussion about this issue.

Several factors must be considered when evaluating data adequacy for allocating the RfD among media. One of the factors to consider is the number of samples in the data set being used to describe a particular exposure medium. Although there are no universal rules about adequate sample sizes, some useful rules of thumb are available. For estimating a 90th percentile value using a non-parametric method, 45 samples are needed, of which at least five must be above detection limits. Fewer samples are usually adequate for estimating mean and median values. In addition to evaluation of sample size, other factors should be assessed for a full evaluation of data adequacy. These factors include representativeness of the sample (e.g., whether sample selection was biased and whether data are current), the accuracy in the sample analysis procedures (i.e., whether errors occurred during measurement), and the sensitivity of the measurement relative to the environmental levels of concern (i.e., whether detection limits are low enough such that the concentration can be detected in most samples within a data set).

As can be seen in Section 5.1.3, above, there are a limited number of studies available to estimate HCBD exposure. Also, the summary statistics and analytical information indicated in the documents reviewed are not always complete. The reasons for using the chosen study for each exposure source (water, food, fish, air) as well as potential problems with these data were addressed in Section 5.1.3. Consideration of the adequacy of exposure data based on the discussion in that section is described here.

Several aspects of the data indicate that they are adequate according to the factors described above. First, both the concentrations of HCBD in drinking water and in fish are taken from studies

with more than 45 samples and are taken from many areas throughout the United States. Enough States have monitored for HCBD in these two media that an estimate of exposure may reasonably be made. In addition, there are enough samples of air concentrations (72) to satisfy the minimum sampling size requirement. However, the geographic extent of the sampling is not indicated. Because the estimate for air exposure is more limited in this respect, it can only be considered indicative of intake in urban areas (or other areas) where the potential for HCBD inhalation exposure exists. It is not possible to make a broader analysis of exposure for the population as a whole. The data on HCBD from non-fish dietary sources are extremely limited. Only one domestic study was found that analyzed for HCBD in dietary foods. However, based on the known uses of HCBD and the extensive discussion with FDA staff, there is reasonable confidence in the exposure estimate of zero.

Another consideration is whether the data are current; in this case, much of the data are fairly old.[9] The concentrations of HCBD in drinking water were measured between 1977 and 1981, the concentrations of HCBD in food were measured prior to 1976, and the air data may be as old as 1970. Although there are reasons to consider some of the data adequate for making some estimates, much of the data are 20 years old and, combined with the overall quantity of samples, this outweighs the positive aspects of the data. Therefore, the data are considered to be "inadequate" according to Box 3 of the Exposure Decision Tree (see the FR notice and TSD for discussion and graphical representation of the Exposure Decision Tree). However, some monitored concentration data are available and, therefore, the data are considered sufficient (according to Box 4) to consider a more conservative allocation of the Pdp/SF among exposure sources.

Sufficient information on the toxicological susceptibility of specific populations (in particular, pregnant women and children) is not available for HCBD. No other particular population is likely to be more highly exposed than another population. Concentrations of HCBD in fish indicate that exposures are not large compared with total exposure. Therefore, sportfishers and subsistence fishers are also not considered particular populations of concern for HCBD. Although infants and children have a higher rate of water and food consumption per body weight compared to adults (USEPA, 1994b), the cancer estimates are based on lifetime exposures and, therefore, the criterion for HCBD is evaluated using exposure factors applicable to adults, who are considered most appropriate for this assessment.

5.3 RSC Estimates/Allocation of the Pdp/SF

After determining that the data are sufficient to make some characterization of exposure along with information regarding its properties and fate in the environment (Box 4 of the Decision Tree approach) and determining that there are multiple exposure sources other than the sources of concern (i.e., other than the drinking water and fish intakes for setting AWQC–Box 8), a more conservative

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[9]*Although many of the samples are not detected (and possibly a reason to consider the data to be inadequate), using different as regarding the values below detection (as shown in Section 5.1.5) doesn't significantly affect the RSC estimates for fish and wate the AWQC.*

allocation of the Pdp/SF is performed (Box 10c). Box 10c potentially allows for either subtracting (as in Box 14) or otherwise allocating the Pdp/SF (as in Box 15), depending on whether there is one or multiple criteria relevant to a chemical in question.

The air exposure is somewhat high compared with the Pdp/SF of 1.8×10^{-4} mg/kg-day. Based on the air intake estimate made, this exposure is 1.20×10^{-4} mg/kg-day (or 67% of the Pdp/SF). Although there are multiple sources of exposure to HCBD, there are no air or dietary health criteria/tolerances relevant to HCBD. In terms of criteria-setting, the sources of concern are drinking water and fish. There is a lifetime health advisory in water (and shorter-term health advisories) for HCBD, however, there is no drinking water MCLG established for HCBD. The assumption made here for the AWQC is that the 2 L/day drinking water intake represents the same quantified intake as would be used for an MCLG. Therefore, a subtraction method (as allowed for in Box 10c) for determining the AWQC is used.[10]

Best Estimate for AWQC

To determine the AWQC for HCBD based on a subtraction method, the amount of each anticipated exposure source other than the source(s) for which the criterion is being set is subtracted from the Pdp/SF. All calculated exposure values are presented in Table 5.1.2. The RSC factor in this case is determined by adding together the estimated intakes from non-fish dietary and air exposures; that is, specifically, 1.20×10^{-4} mg/kg-day. This amount will, in turn, be subtracted from the Pdp/SF of 1.8×10^{-4} mg/kg-day. The leftover amount can be apportioned by accounting for the assumed contributions of drinking water ingestion (2 L/day), the amount of fish ingestion (0.01780 kg/day[11]) and the BAF (1,518, 2,389, and 1,294 L/kg for trophic levels two, three, and four, respectively), so that the amount of HCBD in fish and drinking water that is allowable and that will not exceed the Pdp/SF (in combination with the air contribution) can be determined.

[10]*If the MCLG/HA and the AWQC were considered separately for potential allocations, this would imply a drinking water consu L/day. That is, the drinking water intake would effectively be double-counted. In these instances (where no other criteria are re subtraction method is used instead of a percentage allocation. Refer to the Federal Register notice and TSD for further discussi*

[11] Fish intake rates for each trophic level are: TL2=0.0011 kg/day; TL3=0.0115 kg/day; and TL4=0.0052 kg/day.

Table 5.1.2. Exposure Estimates and Percent of Total Exposure

Exposure source	Exposure Estimate (mg/kg-day)	Percent of Total Exposure	Percent of Pdp/SF
Drinking water (or ambient water) intake	1.43×10^{-6}	1.17	.79
Incidental water intake	7.14×10^{-9}	0.006	.004
Non-fish dietary intake[12]	0	0	0
Fish intake	1.54×10^{-7}	0.126	.09
Air intake	1.20×10^{-4}	98.4	66.7
Total intake	1.22×10^{-4}	100	67.6

Sensitivity Analysis

An alternate estimate of air intake was considered. When Class and Ballschmiter (1987) was used for the estimate of intake from air (because data are recent and because intake from 18 locations was used), exposure from fish and water intake increased to 7 and 66 percent, respectively. Therefore, the choice of air data has a large impact on assumptions about the RSC estimates used in the calculation of AWQC.

5.4 Exposure Intake Parameters

Exposure parameters (e.g., fish intake, drinking water intake, and body weight) chosen for the Ambient Water Quality Criterion equation should reflect the population to be protected. Default exposure factors are available for several specific populations that may be highly exposed or more toxicologically susceptible to a given chemical. A full discussion of these exposure factors are included in Appendix III, Section C of the FR notice (USEPA, 1998a) and in the TSD (USEPA, 1998b). The relevant assumptions on the exposure parameters for HCBD are considered here.

Because no specific population has been identified either toxicologically or by increased exposure, exposure parameters for the general population of adults are used in the Ambient Water Quality Criterion for HCBD. These parameters and their values are as follows:

Fish intake (FI)	0.01780 kg/day
Drinking water intake (DI)	2 L/day (used for drinking water sources)

[12]The central tendency estimate was considered most appropriate for this comparison. The conservative alternate calculation, based on one half of the study detection limit applied to the total diet, results in a theoretical dietary intake of HCBD exceeding the Pdp/SF four-fold.

Incidental ingestion (II)	0.01 L/day (used for non-drinking water sources)
Body Weight (BW)	70 kg

However, if a State or Tribe has identified a specific population of concern other than indicated by this assessment, they have the option to use parameters that reflect exposure for that population.

6. BIOACCUMULATION FACTORS

This section describes the procedures and data sources used to calculate the bioaccumulation factor (BAF) used for deriving an ambient water quality criterion for hexachlorobutadiene. Details and the scientific basis of EPA's recommended methodology for deriving BAFs are described in USEPA (1998a and 1998b). When determining a BAF for use in deriving ambient water quality criteria (AWQCs) for nonpolar organic chemicals, two steps are required. The first step consists of calculating baseline BAFs for organisms at appropriate trophic levels using available field and laboratory studies on the bioaccumulation or bioconcentration of the chemical of interest. Since baseline BAFs are normalized by important factors shown to affect bioaccumulation (e.g., the lipid content of aquatic organisms on which they are based, the freely dissolved concentration of the chemical in water), they are more universally applied to different sites than BAFs not adjusted for these factors. Once baseline BAFs have been calculated for the appropriate trophic levels, the second step involves adjusting the baseline BAFs to reflect the expected conditions at the sites that are applicable to the AWQC (e.g., lipid content of consumed organisms and the freely dissolved fraction of the chemical in the site water). Application of both of these steps to the derivation of a BAF for hexachlorobutadiene is described below.

6.1 Baseline BAF

Different procedures are recommended by EPA for determining the baseline BAF depending on the type of bioaccumulation data available. As described in USEPA (1998b) the data preference for deriving a BAF for non-polar organics is (in order of preference):

1. Calculation of a baseline BAF from a reliable field-measured BAF,
2. Calculation of a baseline BAF from a reliable field-measured biota-sediment accumulation factor (BSAF),
3. Calculation of a baseline BAF from a laboratory-measured bioconcentration factor (BCF) and food-chain multiplier (FCM), and
4. Calculation of a baseline BAF from a predicted BCF and FCM.

Fish consumption rates determined from the USDA's Continuing Survey of Food Intakes by Individuals (CSFII) indicate that on a national, average per capita basis, individuals in the United States consume significant quantities of fish and shellfish at trophic levels two (e.g., clams, oysters), three (e.g., crab, shrimp, flounder) and four (e.g., trout, pike, certain catfish species) (USEPA,

1998c). Therefore, the national AWQC for HCBD requires that baseline BAFs be derived to reflect bioaccumulation in aquatic organisms at each of these three trophic levels. For hexachlorobutadiene, field-measured BAFs of acceptable quality were available for aquatic organisms at trophic levels three and four. Therefore, for trophic levels three and four, field-measured data were used as the preferred choice for deriving the BAFs. For organisms at trophic level two, baseline BAFs were determined using method four, above.

6.1.1 Summary of Field BAF Data

Several field-measured BAFs for HCBD were found in the literature (Table 6.1.1). Residue data from Oliver and Niimi (1983) were collected for adult rainbow trout in Lake Ontario during the spring of 1981 with water column data collected from multiple locations in the fall of 1980. BAF data from Oliver and Niimi (1988) for slimy sculpin are also from Lake Ontario, with water concentration data collected from multiple locations during well mixed conditions in the spring of 1984 and fish tissue data collected during the spring of 1986. BAF data from Burkhard et al. (1997) and Pereria et al. (1988) were collected from different sites within an estuarine-influenced area of Bayou d'Inde in the Calcasieu River, Louisiana. Water column data from Burkhard et al. (1997) represent four 7-day, 24-hour composite samples collected over a one-month period at six stations during the fall of 1990. Fish samples were collected at the end of the water sampling period at the same stations. Average BAFs were determined for each organism based on data from five of the six stations (BAFs from station C were not included because it was believed that water column data did not accurately reflect organism exposure. The resulting BAFs from five stations reflect extensive spatial and temporal averaging which is likely to be important given the likely complex hydrodynamics of the study area.

Water column concentration data from Pereria et al. (1988) used to determine BAFs represent depth-integrated sampling in Bayou d'Inde near an industrial outfall. Although not explicitly stated by Pereria et al. (1988), it appears that the water column concentration of HCBD was based on a single sample taken at this site. Fish residue data used to determine the BAFs by Pereria et al. reflect analysis of 4-6 individuals of four species (Atlantic croaker, spotted sea trout, blue catfish, blue crab) collected at the junction of Bayou d'Inde and the Calcasieu River.

6.1.2 Derivation of Baseline BAF (BAF^{fd})

According to the data preference hierarchy specified above, method 1 was chosen for determining the baseline BAFs. In accordance with this method, each field-measured BAF (expressed as total concentration in tissue divided by total concentration in water) was adjusted to a baseline BAF (expressed as lipid-normalized concentration in tissue divided by freely-dissolved concentration in water) using the following equation:

$$\text{Baseline BAF}^{fd} = \left[\frac{\text{Measured BAF}_T^t}{f_{fd}} - 1 \right] \left(\frac{1}{f} \right)$$

(Equation 6.1.1)

where:

Baseline BAF^{fd}	=	BAF expressed on a freely-dissolved and lipid-normalized basis
Measured BAF_T^t	=	BAF based on total concentration in tissue and water,
f	=	fraction of the tissue that is lipid, and
f_{fd}	=	fraction of the total chemical that is freely-dissolved in the ambient water corresponding to the BAF study.

As described in the TSD (USEPA, 1998b), the freely-dissolved fraction (f_{fd}) of the chemical in water associated with each field-measured BAF was determined using Equation 6.1.2 below.

$$f_{fd} = \frac{1}{[1 + (POC \quad K_{ow}) + (DOC \quad \frac{K_{ow}}{10})]}$$

(Equation 6.1.2)

where:

f_{fd}	=	freely-dissolved fraction of chemical in water associated with the BAF study,
POC	=	concentration of particulate organic carbon (kg/L) associated with the study site,
DOC	=	concentration of dissolved organic carbon (kg/L) associated with the study site, and
K_{ow}	=	n-octanol water partition coefficient for HCBD.

A $\log_{10} K_{ow}$ of 4.842 was estimated for HCBD based on the mean of log K_{ow} values of 4.90 determined by Choiu (1985) and 4.785 determined by Banerjee et al. (1980). Both of these K_{ow} determinations used the shake-flask method. Other parameters used to determine the baseline BAFs from the available field-measured BAFs are shown in Table 6.1.1. BAFs reported by Burkhard et al. (1997) were already expressed on a freely dissolved basis and for a given species, reflect the average of multiple baseline BAFs calculated for individual stations.

Accounting for lipid content and the freely dissolved fraction in determining the baseline BAF (BAF^{fd}) reduces a substantial portion of the overall variability in the BAF_T^ts (e.g., field-measured

BAFs from Pereira et al. (1988) vary by a factor of 25, while baseline BAFs from the same study vary by a factor of four). However, an order of magnitude difference exists between finfish BAF^{fd}s from Pereira et al. (1988) and those from Burkhard et al. (1997), which were measured in the same system. Notably, BAF^{fd}s for blue crab show reasonable agreement between the two studies but are substantially lower than finfish BAF^{fd}s. Burkhard et al. (1997) speculate that lower BAF^{fd}s of blue crab in both studies could be due to differences in chemical metabolism or feeding preferences. Burkhard et al. also suggest that the differences in the finfish BAF^{fd}s between the two studies might reflect the apparent lack of temporal or spatial averaging in water column data collected by Pereria et al. (1988) compared to the extensive averaging conducted in their study.

Further analysis of the data from Pereira et al. (1988) supports this hypothesis. Specifically, HCBD water column concentration data used to determine BAFs by Pereira et al. appear to have been measured at a single site near an industrial outfall in Bayou d'Inde, while tissue concentrations were measured in fish collected at a site located at least one mile further downstream (at the junction of Bayou d'Inde and the Calcasieu River). The mean lipid-normalized HCBD concentrations in blue catfish collected near the industrial outfall (120 ug/g-lipid) is about three times the mean concentration in fish collected at the junction of Bayou d'Inde and the Calcasieu River (46 ug/g-lipid) and over 100 times that measured in fish collected in Lake Charles (1 ug/g-lipid), the furthest site from the outfall. These data suggest a strong gradient in HCBD accumulation in fish as a function of distance from the outfall. Notably, water concentration data for HCBD were only available at the outfall site while residue data were available at three sites only for blue catfish. Due to the greater temporal and spatial averaging of both water and fish tissue data conducted by Burkhard et al. (1997) and the apparent differences in HCBD exposure conditions at the two different sites used to calculate BAFs by Pereira et al. (1988), data from Burkhard et al. (1997) were chosen over those from Pereira et al. (1988) for determining trophic-level specific baseline BAFs.

The trophic-level three baseline BAF is calculated to be 167,695 L/kg-lipid based on the geometric mean of baseline BAFs for blue crab (6,724), mummichog (577,537), Atlantic croaker (283,102), gulf menhaden (342,661), and slimy sculpin (352,036) using data from Burkhard et al. (1997) and Oliver and Niimi (1988). The baseline BAF for trophic-level four is calculated be 43,937 L/kg-lipid (rounded to four significant digits) based on data for rainbow trout determined from Oliver and Niimi (1983). Since the trophic-level three BAF is greater and reflects a potentially greater exposure to consumers of trophic-level three organisms, the trophic-level three baseline BAF was used in calculating the AWQC BAF (below).

For determining a baseline BAF for trophic level two organisms, the following equation was used because acceptable measured data were not found. The scientific basis of this equation is described in (USEPA, 1998b).

$$\text{Baseline BAF}^{fd} = (\text{BCF}^{fd})\ (\text{FCM}) = (K_{ow})\ (\text{FCM})$$

(Equation 6.1.3)

where:

Baseline BAF^{fd}	=	predicted baseline BAF (L/kg-lipid) that, if measured, would reflect the lipid-normalized concentration in the biota divided by the freely dissolved concentration in the water for aquatic organisms at a designated trophic level,
BCF^{fd}	=	Baseline BCF expressed on a freely-dissolved and lipid-normalized basis.
FCM	=	food-chain multiplier reflecting biomagnification at the designated trophic level (unitless), and
K_{ow}	=	octanol-water partition coefficient.

For HCBD, a baseline BAF of 69,502 was calculated for organisms at trophic level two using Equation 6.1.3. A value of 4.842 was selected as a typical $\log_{10} K_{ow}$ value for HCBD based on K_{ow} values reported by Choiu (1985) and Banerjee et al. (1980) as described previously. A FCM of 1.000 was selected based on recommended FCMs for trophic level two organisms described in USEPA (1998b). The calculation of the baseline BAF for trophic level two is shown below.

Trophic Level Two:

$$\text{Baseline } BAF^{fd} = (K_{ow})(FCM2)$$
$$= (10^{4.842})(1.000)$$
$$= 69{,}502$$

Table 6.1.1. Field-Measured Total and Baseline BAFs for Hexachlorobutadiene								
Species	**Size[a]**	**Assigned Trophic Level [b]**	**Total BAF (L/kg-wet wt.)[c]**	**Percent Lipid [d]**	**DOC (POC) mg/L [e]**	**Baseline BAF [f]**	**Log Baseline BAF**	**Data Source**
Rainbow trout *(Oncorhynchus mykiss)*	adults	4 (3-4)	3,274	7.59	2 (0.075)	43,937	4.64	Oliver and Niimi (1983)
Blue crab (*Callinectes sapidus*)	70-235g	3 (2.8-3.4)	NR	0.4-3.4	32-77 (1.9-2.7)	6,724	3.83	Burkhard et al. (1997)
	NR		46.2	0.5	7.7 (1.2)	10,604	4.03	Pereira et al. (1988)
Mummichog *(Fundulus heteroclitus)*	3.0-7.6g	3 (2.8-3.1)	NR	0.6-2.2	32-77 (1.9-2.7)	577,537	5.76	Burkhard et al. (1997)
Atlantic croaker *(Micropogonias undulatus)*	21-26g	3[g]	NR	1.0-3.0	32-77 (1.9-2.7)	283,102	5.45	Burkhard et al. (1997)
	NR		695	2.2	7.7 (1.2)	35,933	4.56	Pereira et al. (1988)
Gulf menhaden *(Brevoortia patronus)*	9.1-12.7g	3 (3.1-3.4)	NR	1.5-3.2	32-77 (1.9-2.7)	342,661	5.53	Burkhard et al. (1997)
Spotted seatrout *(Cynoscion nebulosus)*	NR	4 (3-4)[h]	266	2.3	7.7 (1.2)	13,046	4.12	Pereira et al. (1988)
Blue catfish *(Ictalurus furcatus)*	NR	3	1,170	3.3	7.7 (1.2)	40,317	4.61	Pereira et al. (1988)
Slimy sculpin *(Cottus cognatus)*	8-10g	3 (2.8-3.2)	27,780	8.0	2 (0.0)	352,036	5.55	Oliver and Niimi (1988)

NR = not reported

[a] Weights for Burkhard et al. (1997) are ranges in average organism wet weights from composite samples taken at all stations except station C.

[b] Unless otherwise noted, source of trophic level data is from U.S. EPA (1995a); range of trophic level estimates reported in parentheses.

[c] Total BAFs for Pereira et al. (1988) calculated from author's data; total BAF data from Burkhard et al. (1997) not reported.

[d] Lipid data from Burkhard et al. (1997) are ranges in individual composite samples from all stations except station C.

[e] Carbon data for Pereira taken from USGS (1990). Carbon data from Burkhard et al. (1997) reflect range across all stations except C. Carbon data for Oliver and Niimi (1983, 1988) are from USEPA (1995b).

[f] Baseline BAFs based on lipid-normalized and freely dissolved concentrations calculated using equations 6.1.1 and 6.1.2 and a log K_{ow} of 4.842 for HCBD. Baseline BAFs from Burkhard et al. (1997) determined from averages of baseline BAFs determined for replicate composite samples taken at all stations except C.

[g] source: Mercer (1989).

[h] source: Mercer (1985); Vaughan et al. 1991, Guest and Gunter (1958).

6.2 AWQC BAF

After the derivation of trophic level-specific baseline BAFs for HCBD (described in the previous section), the next step is to calculate BAFs that will be used in the derivation of AWQC. This step is necessary to adjust the baseline BAFs to conditions that are expected to affect the bioavailability of HCBD at the sites applicable to the AWQC. Derivation of the AWQC BAF requires information on: (1) the baseline BAF at appropriate trophic levels, (2) the percent lipid of the aquatic organisms consumed by humans at the site(s) of interest (trophic level specific), and (3) the freely dissolved fraction of the chemical in ambient water at the site(s) of interest. For each trophic level, the equation for deriving a BAF to used in deriving AWQC is:

$$\text{BAF for AWQC}_{(TL\ n)} = [(\text{Baseline BAF}^{fd})_{TL\ n} \quad (f)_{TL\ n} + 1] \quad (f_{fd})$$

(Equation 6.2.1)

where:

BAF for AWQC $_{(TL\ n)}$	=	BAF at trophic level "n" used to derive AWQC based on site conditions for lipid content of consumed aquatic organisms for trophic level "n" and the freely dissolved fraction in the site water
Baseline BAF^{fd} $_{(TL\ n)}$	=	BAF expressed on a freely dissolved and lipid-normalized basis for trophic level "n"
$f_{(TL\ n)}$	=	Fraction lipid of aquatic species consumed at trophic level "n"
f_{fd}	=	Fraction of the total chemical in water that is freely dissolved

Each of the equation components is discussed below.

6.2.1 Baseline BAFs (Baseline BAF^{fd})

The derivation of baseline BAFs at specific trophic levels is described in Section 6.1. For HCBD, baseline BAFs of 69,502, 167,695, and 43,937 L/kg-lipid were determined for aquatic organisms at trophic levels two, three and four, respectively.

6.2.2 Lipid Content of Consumed Aquatic Species (f)

Accumulation of nonpolar organic chemicals in aquatic organisms has repeatedly been shown to be a function of lipid content (e.g., Mackay, 1982; Connolly and Pedersen, 1988; Thomann, 1989). Therefore, baseline BAFs, which are lipid normalized for comparative purposes, need to be adjusted to reflect the lipid content of aquatic organisms consumed by the target population. As discussed in USEPA (1998a, 1998b), EPA recommends that where possible, lipid content of consumed aquatic species be determined on a consumption-weighted average basis.

For the purposes of deriving national ambient water quality criteria, EPA has established national default, consumption-weighted lipid content values of 2.3% at trophic level two, 1.5% at trophic level three, and 3.1% at trophic level four. These national default lipid content values are based on a national survey of fish and shellfish consumption rates and information on their lipid content (see USEPA 1998a, 1998b for details of the determination of national default lipid content values). As discussed in the FR notice and TSD (USEPA, 1998a, 1998b), EPA considers the use of national default lipid values as being appropriate in situations where local or regional data on lipid content and consumption rates are unavailable for the site(s) applicable to the AWQC. However, if local or regional data are available for the site(s) of interest, EPA recommends that States and Tribes use the local or regional data instead of the national default values because the type and quantity of consumed aquatic organisms and their lipid content may vary from one location to another.

6.2.3 Freely-Dissolved Fraction Applicable to AWQC

Information on the freely-dissolved fraction of the chemical expect at the site(s) applicable to the AWQC is important because the freely dissolved form of nonpolar organic chemicals is considered to represent the most bioavailable form in water and thus, the form that best predicts bioaccumulation (USEPA 1998a, 1998b). Freely dissolved chemical is defined as the portion of the chemical dissolved in water, excluding the portion sorbed on to particulate and dissolved organic carbon. The freely-dissolved fraction is estimated from the octanol-water partition coefficient and the dissolved and particulate organic carbon concentrations as shown below.

$$f_{fd} = \frac{1}{[1 + (POC \quad K_{ow}) + (DOC \quad \frac{K_{ow}}{10})]}$$

(Equation 6.2.2)

where:

f_{fd}	=	freely-dissolved fraction of chemical in water applicable to the AWQC
POC	=	concentration of particulate organic carbon applicable to the AWQC (kg/L)
DOC	=	concentration of dissolved organic carbon applicable to the AWQC (kg/L)
K_{ow}	=	n-octanol water partition coefficient for the chemical

In this equation, the terms "K_{ow}" and "$K_{ow}/10$" are used to estimate the partition coefficients to POC and DOC, respectively, which have units of L/kg, the scientific basis of which is explained in USEPA (1998b). Based on national default values of 2.9 mg/L for DOC, 0.48 mg/L for POC, and 69,502 for the K_{ow} ($Log_{10} K_{ow}$ of 4.842), the freely dissolved concentration of HCBD is calculated to be 0.9492 (expressed as four significant digits for convenience). Calculation of the default freely dissolved concentration is provided below.

$$f_{fd} = \frac{1}{[1 + (POC \quad K_{ow}) + (DOC \quad \frac{K_{ow}}{10})]}$$

$$f_{fd} = \frac{1}{[1 + (4.8 \times 10^{7} \text{ kg/L} \quad 69{,}502 \text{ L/kg}) + (2.9 \times 10^{6} \text{ kg/L} \quad \frac{69{,}502}{10} \text{ L/kg})]}$$

$f_{fd} = 0.9492$

The national default values for POC and DOC used here are based on the median value of POC and DOC concentrations observed in numerous water bodies across the United States and are described further in USEPA (1998a, 1998b). For the purposes of deriving national AWQC, EPA believes that the use of national default values is appropriate. In addition, EPA considers the use of national default values of POC and DOC as being appropriate in situations where local or regional data on POC and DOC are unavailable for the site(s) applicable to the AWQC. However, if local or regional data are available for the site(s) of interest, EPA recommends that States and Tribes use the local or regional data instead of the national default values because the POC and DOC can vary on a local basis, thus affecting the freely dissolved fraction.

6.2.4 Calculation of AWQC BAF

Using Equation 6.2.1 above, BAFs appropriate for calculating national AWQC for HCBD are: 1518, 2389, 1294 L-kg tissue for organisms at trophic levels two, three and four, respectively (expressed as four significant digits for convenience). These BAFs were derived using baseline BAFs of 69,502, 167,695, and 43,937 L/kg-lipid for the baseline BAF at all three trophic levels, percent lipid content values of 2.3%, 1.5%, and 3.1% at trophic levels two, three, and four, respectively, and a freely dissolved fraction of 0.9492. Calculation of the AWQC BAFs are shown below.

$$\text{BAF for AWQC}_{(TL\ n)} = [(\text{Baseline BAF}^{fd})_{TL\ n} \quad (f)_{TL\ n} + 1] \quad (f_{fd})$$

AWQC BAF for Trophic Level Two

= [(69,502 L/kg-lipid)•(0.023) +1] • (0.9492)

= 1518 L/kg-tissue (expressed as four significant digits for convenience)

AWQC BAF for Trophic Level Three

= [(167,695 L/kg-lipid)•(0.015) +1] • (0.9492)

= 2389 L/kg-tissue (expressed as four significant digits for convenience)

AWQC BAF for Trophic Level Four

= [(43,937 L/kg-lipid)•(0.031) +1] • (0.9492)

= 1294 L/kg-tissue (expressed as four significant digits for convenience)

7. AWQC CALCULATION

7.1 For Ambient Waters Used as Drinking Water Sources

7.1.1 Calculation Using the New Linear Approach

The cancer-based AWQC was calculated using the RSD derived above and other input parameters listed below:

$$AWQC = RSD \times \left(\frac{BW}{DI + \sum_{i=2}^{4} (FI_i \times BAF_i)} \right)$$

(Equation 7.1.1)

where:

RSD	=	Risk specific dose 2.5 x 10^{-5} mg/kg-day (for 10^{-6} risk) (see Section 4.2.5.3)
BW	=	Human body weight assumed to be 70 kg
DI	=	Drinking water intake assumed to be 2 L/day
FI_i	=	Fish intake at trophic level i, i=2, 3, and 4; total intake assumed to be 0.01780 kg/day[13]
BAF_i	=	Bioaccumulation factor at trophic level i (i=2, 3, and 4) equal to 1,518 L/kg-tissue for trophic level two; 2,389 L/kg-tissue for trophic level three; and 1,294 L/kg-tissue for trophic level four

This yields an AWQC value of 4.6 x 10^{-5} mg/L (or 0.046 g/L rounded from 0.0462 g/L).

[13] Fish intake rates for each trophic level are : TL2=0.0011 kg/day; TL3=0.0115 kg/day; and TL4=0.0052 kg/day (presented as four significant figures for convenience). See Section 2.4.8 of the TSD for more information.

7.1.2 Calculation Using the MOE Approach

The AWQC using the MOE approach is calculated using the following equation and the input parameters listed below[14]:

$$AWQC = \left(\frac{Pdp}{SF} - RSC_{air} \right) x \left(\frac{BW}{DI + \sum_{i=2}^{4} (FI_i \; x \; BAF_i)} \right)$$

(Equation 7.1.2)

where:

Pdp	=	Point of departure (i.e., LED_{10}, LOAEL, or NOAEL based on precursor effect). Here it is 0.054 mg/kg-day (human equivalent)
SF	=	Safety factor of 300
RSC	=	Relative source contribution from air assumed to be 1.2 x 10^{-4} mg/kg-day
BW	=	Human body weight assumed to be 70 kg
DI	=	Drinking water intake assumed to be 2 L/day
FI_i	=	Fish intake at trophic level i, i=-2, 3, and 4; total intake assumed to be 0.01780 kg/day [15]
BAF_i	=	Bioaccumulation factor at trophic level i (i=2, 3, and 4) equal to 1,518 L/kg-tissue for trophic level two, 2,389 L/kg-tissue for trophic level three, and 1,294 L/kg-tissue for trophic level four

This yields an AWQC of 1.1 x 10^{-4} mg/L, or 0.11 g/L. [16]

[14]For a calculation that involves subtracting background exposures other than those for drinking water and fish ingestion, it is easier to express the equation so that the RSC factor (in this case, the background air exposure) is subtracted first from the Pdp/SF since they are both in units of mg/kg-day. By doing this, the adjustments for body weight, the fish and drinking water intakes, and the BAF are more straightforward. For further discussion, refer to the *Federal Register* notice or the TSD.

[15]Fish intake rates for each trophic level are TL2=0.0011 kg/day; TL3=0.0115 kg/day; and TL4=0.0052 kg/day (presented as four significant figures for convenience).

[16] The difference between the observed response and the estimated human exposure for HCBD, known as the MOE, indicates a slightly greater than three-log difference. Given that there is significant uncertainty in the exposure estimate, the ratio is: 0.054 mg/kg-day÷1.22 x 10^{-4} mg/kg-day =442.6.

7.2 For Ambient Waters Not Used as Drinking Water Sources

When the waterbody is to be used for recreational purposes and not as a source of drinking water, the drinking water value (DI above) is eliminated from the equations shown above for both the MOE and new linear approaches. It is substituted with an incidental ingestion value. The incidental intake is assumed to occur from swimming and other activities. The fish intake value is assumed to remain the same. The default value for incidental ingestion is 0.01 L/day.

7.2.1 Calculation Using the New Linear Approach

When the equation shown above in Section 7.1.1 is used to calculate the AWQC with the substitution of an incidental ingestion of 0.01 L/day, an AWQC of 4.9×10^{-5} mg/L (or 0.049 g/L, rounded from 0.0487 g/L) is obtained.

7.2.2 Calculation Using the MOE Approach

When the equation shown above in Section 7.1.2 is used to calculate the AWQC with the substitution of an incidental ingestion of 0.01 L/day, an AWQC of 1.2×10^{-4} mg/L (or 0.12 g/L, rounded from 0.117 g/L) is obtained.

7.2.3 AWQC Summary

Table 7.2.1 contains a summary of the AWQC calculated using the linear and nonlinear approaches. The nonlinear approach utilizes a relative source contribution factor in the calculation of the AWQC. Note that due to the BAF, the contribution to intake from drinking water is relatively small; consequently, the AWQC for both fish/shellfish consumption only and fish/shellfish and drinking water consumption uses are not significantly different.

Table 7.2.1: Summary of AWQC Values Obtained Using Linear and Nonlinear Approaches			
Nonlinear Approach: all water uses, and other exposures[17]	**Nonlinear Approach: fish/shellfish consumption only, and other exposures**	**Linear Approach: all water uses[18] (10^{-6} risk)**	**Linear Approach: fish/shellfish consumption only (10^{-6} risk)**
0.11 g/L	0.12 g/L	0.046 g/L	0.049 g/L

As indicated earlier, the cancer studies are extremely limited. The only observation of cancer is in the kidney, which is also the site of renal toxicity. There are indications of renal toxicity below and at the levels at which carcinogenicity is seen. Carcinogenesis appears to be secondary to the renal toxicity. EPA is, therefore, recommending an AWQC based on the nonlinear approach.

8. SITE-SPECIFIC OR REGIONAL ADJUSTMENTS TO CRITERIA

Several parameters in the AWQC equation can be adjusted on a site-specific or regional basis to reflect regional or local conditions and/or specific populations of concern. These include fish consumption; incidental water consumption as related to regional/local recreational activities; BAF (including factors used to derive BAFs such as POC/DOC, percent lipid of fish consumed by target population, and species representative of given trophic levels); and the relative source contribution. States and Tribes are encouraged to make adjustments using the information and instructions provided in the Technical Support Document (USEPA, 1998b).

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[17] "All water uses" indicates both drinking water and fish/shellfish consumption uses of water. "Fish/shellfish consumption only" indicates the waterbody is not used as a source of drinking water; however, it does include an incidental water intake of 0.01 L/day from recreational activities. The nonlinear approach also incorporates a relative source contribution (RSC) that assumes, in this case, a contribution to exposure of 1.2×10^{-4} from air (see the equation shown in Section 7.1.1).

[18] The linear approach does not include an RSC, and the AWQC derived using this method considers only exposures from water.

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